PATENT

Docket No. 26294005US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Attila T. LORINCZ, et al. Group Art Unit: 1631

Serial No : 09/210,031 Examiner: BRUSCA, J.

Filed : December 11, 1998

For : **UNIVERSAL COLLECTION MEDIUM**

DECLARATION UNDER 37 C.F.R. §1.132

Box AF
Commissioner of Patents
Washington, D.C. 20231

Sir:

This is a Declaration under 37 C.F.R. §1.132 by Dr. Attila T. Lorincz in the above-identified application.

I, the undersigned, Attila T. Lorincz, Ph.D., declare and state that:

1. My education and professional experience as an expert in the area of nucleic acid chemistry and analysis are set forth on the attached copy of my Curriculum Vitae (Exhibit A).

2. As stated on my Curriculum Vitae, my area of expert training and experience is in nucleic acid chemistry, in the analysis of nucleic acids in biological samples, and in the use of such nucleic acid analyses to develop diagnoses and prognoses concerning diseases related to the organism from which the nucleic acid was obtained.

3. I have read and understand the Office Action dated April 5, 2002, issued in the above-identified application. I have read and understand the above-identified

patent application and the pending claims.

4. I understand that the Examiner considers the composition reported at column 6, lines 8-61 and in Example 4 of Dunphy U.S. Patent No. 5,679,333 to make obvious the composition described in claims 36-74 of the above-identified application.

5. It is my opinion, as an expert in the field of nucleic acid chemistry and analysis, that the composition described in Dunphy does not make obvious the composition described in claims 36-74 of the above-identified application because the composition of Dunphy does not make possible the direct analysis of cells contained in the composition by both cytological analysis and molecular analysis of DNA, RNA, or protein.

6. Evidence establishing that the Dunphy composition of Example 4 does not properly preserve DNA and RNA, and thus make possible the direct molecular analysis of cells according to the subject claims, is provided by the following experimental results using the Dunphy composition to analyze cellular DNA and RNA.

7. The solution described in Dunphy Example 4 was prepared in three different ways ('Dunphy 1', 'Dunphy 2' and 'Dunphy 3') as follows and used in the molecular analyses described below:

Dunphy 1

Ethanedial (also known as glyoxal)	3.75% v/v
Ethanol	20.0% v/v
Polyethylene Glycol (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide	0.0275% v/v
Water	72.7% v/v

Dunphy 2

pH 7: The pH was adjusted according to the instructions provided by the Dunphy patent, "The solution typically has a relatively acidic pH, but may be buffered to a substantially neutral pH (e.g. within the range of about 6.8 to about 7.8). The addition of approximately 4 grams acid sodium

phosphate monohydrate and 6.5 grams disodium phosphate (anhydrous) per liter of solution generally is effective to buffer the solution within this preferred pH range)." (at column 6, lines 16-22)

Ethanedial (also known as glyoxal)	3.75% v/v
Ethanol	28.0% v/v
Polyethylene Glycol (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide	0.0275% v/v
Water	63.2% v/v
Acid Sodium Phosphate	0.4% w/v
Disodium Phosphate	0.65% w/v

Dunphy 3

pH 7: The pH was adjusted according to the instructions provided by the Dunphy patent as stated above.

Ethanedial (also known as glyoxal)	3.75% v/v
Ethanol	20.0% v/v
Polyethylene Glycol (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide	0.0275% v/v
Water	71.2% v/v
Acid Sodium Phosphate	0.4% w/v
Disodium Phosphate	0.65% w/v

8. The following composition described in the subject application ("UCM") was prepared as follows and used in the molecular analyses described below:

Butanol	9% v/v
PEG (MW 1450)	2% w/v
Sodium Azide	0.05% w/v
EDTA	5 mM
Sodium Acetate-Acetic Acid	10 mM
pH	4.5

9. Cultured, Human Papilloma Virus (HPV)-16-positive CaSki cells and HPV-negative Jurkat cells were used to examine whether or not the Dunphy compositions preserve and make possible the direct analysis of nucleic acid.

10. The direct analyses of nucleic acids were conducted by following the method for detecting DNA and RNA by the Digene Hybrid Capture (HC) method, described in WO 93/10263 by Digene Corporation. Briefly, after the media compositions

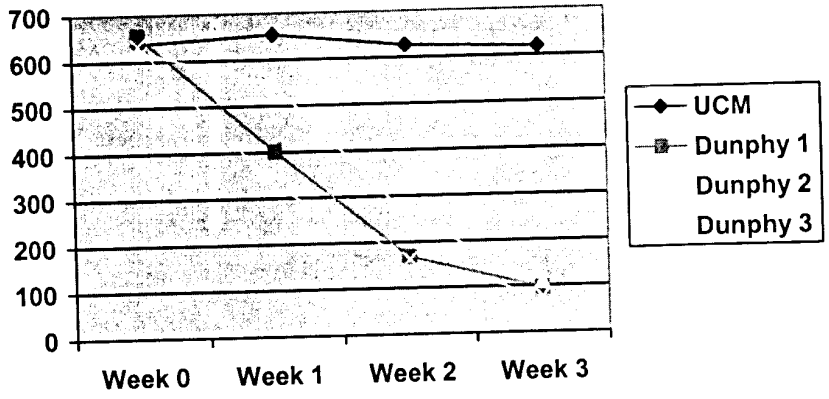
were spiked with cells, the cells were lysed and probe mix was added to each sample. For the HPV DNA assay the probe mix contained an RNA probe specific to genomic HPV DNA. For the HPV RNA assay the probe mix contained a single-stranded biotinylated DNA probe specific to HPV E6 and E7 RNA. The plate was sealed and incubated at 65°C for 1.5 hours for hybridization of the probes to HPV E6 and E7 RNA or genomic HPV DNA to occur. After hybridization, samples were transferred into wells of a microplate coated with anti-hybrid polyclonal antibody in the DNA assay or with streptavidin in the RNA assay. To each well, 25 µl of anti-hybrid detection antibody was added. The plate was agitated at 1100 RPM, for 1 hour, at room temperature. Wells were washed six times with wash buffer. 100 µl of a chemiluminescent substrate was added to each well and the plate was incubated at room temperature for 30 minutes. The plate was then read in the Digene Microplate 2000 Luminometer. The data was then expressed as a signal-to-noise ratio. These assays test the efficacy of preservation media as specific signal is obtained only when DNA or RNA is not degraded, since signal is contingent upon the hybridization of probes to non-degraded DNA or RNA.

11. The Dunphy 1, 2 and 3 compositions and the UCM (Digene) composition were tested using the HC II HPV DNA test. A standard HC II HPV Test kit (Digene catalog number 5101-1069) was used. Each tested composition was spiked with 10000 cells/ml (Table 1) and 1000 cells/ml (Table 2) of CaSki cell concentrations. The HC II test was performed at day 0 (baseline) and after one, two and three weeks of storage at room temperature. The HPV negative Jurkat cell samples were used to test the background noise.

12. Table 1. Hybrid Capture II DNA assay Signal to Noise (S/N) ratios obtained for the samples of the three Dunphy compositions and UCM at 10,000 cells/ml of CaSki cells

	Week 0	Week 1		Week 2		Week 3	
Medium	Baseline S/N	S/N	S/N as % of Baseline	S/N	S/N as % of Baseline	S/N	S/N as % of Baseline
UCM Control	637	654	103	626	98	619	97
Dunphy 1	655	401	61	168	26	96	15
Dunphy 2	621	547	88	254	41	109	18
Dunphy 3	633	326	52	162	26	77	12

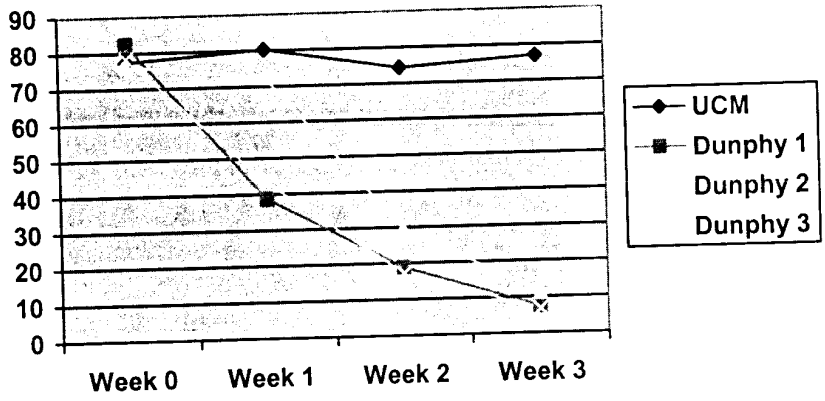
13. Chart 1: Graph of Table 1 Data: The Y-axis values are the S/N ratios. The X-axis values are time.



14. Table 2: Hybrid Capture II DNA Assay - S/N Ratio Obtained for Samples Containing 1000 cells/ml of CaSki cells.

	Week 0	Week 1		Week 2		Week 3	
Medium	Baseline S/N	S/N	S/N as % of Baseline	S/N	S/N as % of Baseline	S/N	S/N as % of Baseline
UCM Control	77.4	80.2	104	74.3	96	76.9	99
Dunphy 1	82.3	38.7	47	18.9	23	7.5	9
Dunphy 2	76.2	72.5	95	29.6	39	11.3	15
Dunphy 3	78.3	43.2	55	17.2	22	6.7	9

15. Chart 2: Graph of Table 2 Data. The Y-axis values are the S/N ratios. The X-axis values are time.



16. The data in Table 1 and Table 2 show that at time 0, i.e. at week 0 (baseline), all tested Dunphy compositions had comparable S/N ratios with the UCM control. However, the positive signal for Dunphy's compositions significantly dropped as time progressed (see Charts 1 and 2). After storage of the cells in Dunphy's compositions for three weeks, only 10-20% of the original positive signals were preserved. The UCM sample retained its signal after three weeks (97-99% of baseline signal).

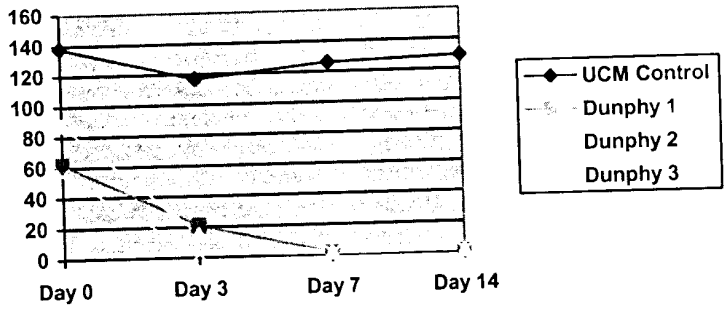
17. Similarly, RNA analysis of the samples was performed following the general principles of the Hybrid Capture method described in WO 93/10263. The

Dunphy 1, 2 and 3 compositions and the UCM (Digene) composition were tested using the HC II HPV RNA test. Each tested composition was spiked with 10000 cells/ml (Table 3) and 1000 cells/ml (Table 4) of CaSki cell concentrations. The HC II test was performed at day 0 (baseline) and after three, seven and fourteen days of storage at room temperature. The HPV negative Jurkat cell samples were used to test the background noise.

18. Table 3. Hybrid Capture II RNA assay signal to noise ratios obtained for samples with 10,000 cells/ml of CaSki cells.

Medium	Baseline S/N (Day 0)	Day 3 S/N	Day 3 S/N as % of Baseline	Day 7 S/N	Day 7 S/N as % of Baseline	Day 14 S/N	Day 14 S/N as % of Baseline
UCM Control	138	117	85%	126	91%	129	94%
Dunphy 1	62	21	34%	1.5	7%	0.9	4%
Dunphy 2	88	15	17%	1.4	9%	1.1	7%
Dunphy 3	55	2.2	4%	0.9	2%	1.0	2%

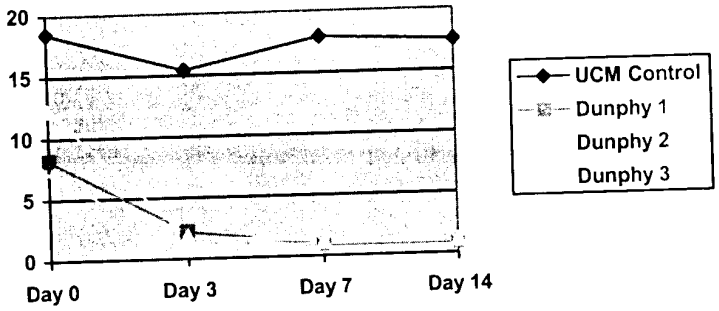
19. Chart 3: Graph of Table 3 Data. The Y-axis values are the S/N ratios. The X-axis values are time.



20. Table 4. Hybrid Capture II RNA assay signal to noise ratios obtained for samples with 1000 cells/ml of CaSki cells.

Medium	Baseline S/N (Day 0)	Day 3 S/N	Day 3 S/N as % of Baseline	Day 7 S/N	Day 7 S/N as % of Baseline	Day 14 S/N	Day 14 S/N as % of Baseline
UCM Control	18.5	15.4	83%	17.9	97%	17.5	95%
Dunphy 1	8.2	2.2	27%	0.9	11%	0.9	11%
Dunphy 2	12.3	1.8	15%	1.2	10%	1.1	9%
Dunphy 3	7.1	0.9	13%	1.0	14%	1.0	14%

21. Chart 4: Graph of Table 4 Data. The Y-axis values are the S/N ratios. The X-axis values are time.



22. The results of Table 3 and 4 demonstrate that all of the Dunphy compositions had a significantly lower S/N ration than UCM control at baseline, and the positive signal was significantly degraded after storage of the sample at room temperature for 3 to 7 days. The UCM samples retained their signal after two weeks.

23. Thus, all tested compositions based on Dunphy's Example 4 formulation for tissue preservation did not preserve the HPV DNA or RNA properly for the hybrid capture HPV assays. Charts 1-4 markedly show that the Dunphy-based compositions are not able to preserve the integrity of DNA or RNA, as the S/N ratios decrease significantly in relation to time. In contrast, as reported in the instant application, the UCM composition properly preserves both the DNA and RNA for hybrid capture assays. The preservation capability of the UCM formulation is apparent as the signal to noise ratio does not decrease over time for

both DNA and RNA analysis.

24. Further, in view of the published data in the art and my experience in the field of nucleic acid chemistry, the addition of EDTA to Dunphy's medium would not likely improve RNA stability in this medium. Dunphy's medium was formulated to preserve cellular morphology for histological examination and clearly did not anticipate a medium that would in addition preserve DNA and RNA integrity. We have demonstrated a clear advantage in RNA and DNA stability with UCM compared to Dunphy's Example 4 medium. EDTA would likely impede bacterial growth which is the only motivation for its use in Dunphy's Example 4 medium, but it would be unlikely that it would be anticipated to improve RNA stability. Furthermore, there is no reference in Dunphy for the use of EDTA to prevent DNA degradation, nor was it obvious to add EDTA for this purpose. EDTA functions as a chelator with high affinity for magnesium and other metal ions. These metals are not required for most RNAse enzymes.

25. Not all DNA nucleases require metal cofactors and therefore not all DNA nucleases are inhibited by EDTA. For example, the Nuc endonuclease, encoded by the IncN plasmid pKM101 present in *Salmonella typhimurium*, is not inhibited by EDTA (Zhao et al *Protein Science* (1997), *6*: 2655-26580). The abstract from this article states: "The recombinant enzyme was able to hydrolyze both double and single-strand DNA and an artificial substrate, bis(4-nitrophenyl) phosphate, which contains a phosphodiester bond. The enzyme activity was not inhibited in the presence of EDTA and was not regulated by divalent cations."

26. EDTA is not even considered in the art as a general ribonuclease inhibitor. The three websites listed below all state the general ineffectiveness of EDTA for inhibition of ribonuclease activity: (1) the Ambion website, http://www.ambion.com/techlib/append/nuclease.html; (2) the New England Biolabs website, http://www.neb.com/neb/frame_cat.html; and (3) the Promega website, http://www.promega.com/pnotes/63/8581_17/promega.html.

27. I declare further that all statements made on information and belief are believed to be true, and, further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Respectfully submitted,

Date : June 24, 2002

Attila T. Lorincz, Ph.D.

Curriculum Vitae

ATTILA T. LÖRINCZ, PH.D.

Address: **Work:** Digene Corporation
1201 Clopper Road
Gaithersburg, MD 20878
Phone: 301-944-7350
E-mail: ATTILA.LORINCZ@DIGENE.COM

Home: 6 Chinaberry Court
North Potomac, MD 20878
Phone: 301-869-2404

University Education:

Graduate, 1976-1979 Department of Genetics, Trinity College, Dublin, Ireland.
Ph.D., 1980. Research project: Investigation of cell size and cell division control in *Saccharomyces cerevisiae*.

Undergraduate, 1972-1976 University College, Dublin, Ireland.
B.Sc., Honors 1976. Microbiology (major), Biochemistry (minor).
Research project: Characterization of an α-amylase of *Pseudomonas saccharophila*.

Professional Positions:

Senior Vice President and Chief Scientific Officer, since 2000. Digene Corporation, Gaithersburg, Maryland 20878.
Report directly to company President and CEO. Responsibilities include: key role in company policy decision-making at the executive committee level; speaking at scientific meetings worldwide as an acknowledged expert on human papillomaviruses and genetic testing; instigating and supervising basic scientific research; collaborating with scientists worldwide in studies published in prestigious peer-reviewed journals; evaluating Digene's position on intellectual property; evaluating new technology in other laboratories for possible licensing or other use by Digene; representing Digene and its technology at business meetings worldwide.

Vice President, R&D, and Scientific Director, 1990-1999.
Responsibilities included: supervision and guidance of up to 40 scientists, long-range scientific planning for the company, review of detailed research plans, assurance of quality results, and timely achievement of company R&D goals. Principal areas of research focus were the development of diagnostic nucleic acid probe tests for a broad range of human infectious diseases, cancers, and inherited disorders. Other responsibilities included the planning and coordination of clinical studies, U.S. Food and Drug Administration submissions, and interactions with high-level biomedical consultants and collaborators from universities and other companies.

Lecturer, 1999. Zanvyl Krieger School of Arts and Sciences, Johns Hopkins University, Montgomery County Center, Rockville, MD 20850.
Designed and taught a new course in the history of medical diagnostics for candidates for the M.A. in Biotechnology.

Adjunct Associate Professor, 1989-present. Department of Pathology, Georgetown University Medical School, Washington, DC 20007.
Research efforts focused on human papillomaviruses, with particular emphasis on diagnostic applications, and on molecular mechanisms of carcinogenesis in human keratinocytes. Other projects involved the study of tumor suppressor genes and their use as markers for cancer prognosis.

Scientific Director, Corporate Research, 1989-1990. Life Technologies, Inc., Gaithersburg, Maryland. Studied *in vitro* transcription, transgenic animals, and other model systems of interest to research scientists for the purpose of generating research reagents.

Section Head of Advanced Molecular Diagnostics, 1984-1989. Life Technologies, Inc. Gaithersburg, Maryland. Investigated medical and molecular aspects of the human papillomavirus.

Research Scientist, 1982-1984. University of California at Santa Barbara. Investigated regulation and organization of *S. cerevisiae* genes involved in cell cycle control.

Research Scientist, 1980-1982. University of California at San Diego. Performed quantitative computer analyses of protein regulation during the cell cycle of *S. cerevisiae*, using two-dimensional gel electrophoresis.

Honors And Other Professional Activities:

High Technology Council of Maryland Award for Biotechnology Product of the Year 2000, awarded to the Hybrid Capture® II HPV DNA Test.

American Venereal Disease Association A.V.D.A. Achievement Award 1994, presented in recognition of outstanding contributions toward the control of sexually transmitted diseases.

Primary author of cell cycle paper in Nature, 1984.

Senior author of papers in JAMA, 2000, detailing the role of HPV in cervical cancer screening.

Editorial board member of IVD Technology and of Clinical and Diagnostic Virology.

Scientific and medical reviewer for: Obstetrics and Gynecology, Science, Journal of Clinical Microbiology, Journal of General Virology, Clinical and Diagnostic Virology, and others.

Peer reviewer for the National Institutes of Health, since 1986.

Life Technologies, Inc., David L. Coffin Award for Technical Innovation, for developing the FDA approved HPV test ViraPap®, 1989.

Life Technologies, Inc., David L. Coffin Patent Award, for human papillomavirus 56 nucleic acid hybridization probes and methods for employing same, US Patent No. 4,908,306.

Irish Department of Education Ph.D. Scholarship Recipient, 1976-1979.

National Clinical Trials:

Co-principal investigator for HPV QC Group in the NCI ALTS study to investigate alternatives in women's health care for managing cervical disease. Contract NCI-CN-55044-07, awarded 1995.

Federal Research Grants:

Principal Investigator for Contract N44-AI-85335, "Rapid Detection and Typing of HSV DNA." SBIR Phase II grant from NIAID, awarded May, 1998.

Principal Investigator for Contract N43-AI-45214, "Rapid Detection and Typing of Herpes Simplex virus (HSV) DNA in Clinical Specimens." SBIR Phase I grant from NIAID, completed 1996.

Subcontract MA-5623-26 with Microbiological Associates, Inc., "Assays to Detect and Type Human Papillomavirus DNA in Cervical Lavage Samples." Completed 1995.

Patents:

US patent nos. 4,849,331; 4,849,332; 4,849,334; and 4,908,306 for the use of HPV types 35, 43, 44, and 56 in diagnostic testing.

US patent nos. 5,981,179 and 6,027,897 and Australian patent no. 711130 for CAR target amplification technology.

Australian patent no. 673813 for Hybrid Capture® technology.

Other patents pending for Hybrid Capture® technology.

Memberships:

American Society for Microbiology (since 1980)

Pan American Group for Rapid Viral Diagnosis (since 1986)

American Association of Clinical Chemistry (since 1991)

International Committee on HPV Nomenclature (1986-1991)

International Conferences

Dr. Lörincz has been an invited speaker at many international conferences, a list of which is available on request.

Departmental Seminars

Dr. Lörincz has been an invited speaker at many departmental seminars, a list of which is available on request.

Managerial Experience:

- Head of several scientific teams, with full responsibilities for project planning, budgets, hiring, promotions, data analyses, presentations, publications, etc. Principal investigator for numerous clinical studies. As a member of the executive staff of Digene, I am intimately involved in setting overall company objectives and policies.

- Head of several multi-disciplinary strategic planning teams involving R&D, Regulatory Affairs, Marketing and Sales, Development, and Manufacturing.

- Director of Intellectual Property for Digene Corporation, 1990-1994. Prepared patent applications with assistance of attorneys.

- Played a major role in preparing several PMA applications for Life Technologies' and Digene's HPV testing kits. Presented data to FDA panels, leading to successful approval of the ViraType® and Hybrid Capture® kits for detecting and typing HPV DNA.

- Key member of the Executive Committee directing a successful initial public offering of Digene Corporation on NASDQ in May, 1996, and a secondary offering in October, 1997.

SELECTED PUBLICATIONS

Dr. Lörincz has 72 peer-reviewed scientific publications prior to 1995, a list of which is available on request. A list of peer-reviewed publication since 1995 follows:

Schiffman, M.H., N.B. Kiviat, R.D. Burk, K.V. Shah, R.W. Daniel, R. Lewis, J. Kuypers, M.M. Manos, D.R. Scott, M.E. Sherman, R.J. Kurman, M.H. Stoler, A.G. Glass, B.B. Rush, I. Mielzynska, and **A.T. Lorincz** (1995) Accuracy and interlaboratory reliability of human papillomavirus DNA testing by Hybrid Capture. J. Clin. Microbiol. 33:545-550.

Cox, J.T., **A.T. Lorincz**, M.H. Schiffman, M.E. Sherman, A. Cullen, and R.J. Kurman (1995) Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am. J. Obstet. Gynecol. 172(3):946-954.

Reid, R., and **A.T. Lörincz** (1995) Human papillomavirus tests. In: Ballière's Clinical Obstetrics and Gynaecology (H.W. Jones, III, guest ed.), vol. 9, no. 1, pp. 63-103. Ballière Tindall, London.

Lorincz, A. (1995) Hybrid Capture™: A simple, sensitive method for the routine detection of HPV DNA. In: Screening of Cervical Cancer: For Whom, Why and How? Experts' Conference. 2nd International Congress of Papillomavirus in Human Pathology. Paris, France, Unesco, April 6, 7, 8, 1994 (Monsonego, J., ed.), pp. 59-62. EUROGIN Scientific Publications, Paris.

Wideroff, L.; Schiffman, M.H.; Nonnenmacher, B.; Hubbert, N.; Kirnbauer, R.; Greer, C.E.; Lowy, D.; **Lorincz, A.T.**; Manos, M.M.; Glass, A.G.; Scott, D.R.; Sherman, M.E.; Kurman, R.J.; Buckland, J.; Tarone, R.E.; Schiller, J (1995) Evaluation of seroreactivity to human papillomavirus type 16 virus-like particles in an incident case-control study of cervical neoplasia. J. Infect. Dis. 172(6):1425-1430.

Lörincz, A. (1995) Human papillomaviruses. In: Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections, 7th edition (Lennette, E.H., et al., eds.), pp. 465-480. American Public Health Association, Washington, D.C.

Lörincz, A. (1996) Hybrid Capture™ method for detection of human papillomavirus DNA in clinical specimens. Papillomavirus Report 7(1):1-7.

Reid, R.; **Lörincz, A.** (1996) New generation of human papillomavirus tests. In: Cervical Cancer and Preinvasive Neoplasia (Rubin, S.C.; Hoskins, W.J., eds.), pp. 27-47. Lippincott-Raven, Philadelphia.

Lörincz, A.T. (1996) Molecular methods for the detection of human papillomavirus infection. In: Obstetrics and Gynecology Clinics of North America: The Papillomaviruses, 2nd edition (Lörincz, A.T.; Reid, R., eds.), vol. 23, no. 3, pp. 707-730. W.B. Saunders, Philadelphia.

Tsukui, T.; Hildesheim, A.; Schiffman, M.H.; Lucci, J., III; Contois, D.; Lawler, P.; Rush, B.B.; **Lorincz, A.T.**; Corrigan, A.; Burk, R.D.; Qu, W.; Marshall, M.A.; Mann, D.; Carrington, M.; Clerici, M.; Shearer, G.M.; Carbone, D.P.; Scott, D.R.; Houghten, R.A.; Berzofsky, J.A. (1996) Interleukin 2 production *in vitro* by peripheral lymphocytes in response to human papillomavirus-derived peptides: correlation with cervical pathology. Cancer Res. 56(17):3967-3974.

Hall, S.; **Lörincz, A.**, Shah, F.; Sherman, M.E.; Abbas, F.; Paull, G.; Kurman, R.J.; Shah, K.V. (1996) Human papillomavirus DNA detection in cervical specimens by Hybrid Capture: correlation with cytologic and histologic diagnoses of squamous intraepithelial lesions of the cervix. Gynecol. Oncol. 62:353-359.

Wideroff, L.; Schiffman, M.H.; Hoover, R.; Tarone, RE; Nonnenmacher, B.; Hubbert, N.; Kirnbauer, R.; Greer, C.E.; **Lorincz, A.T.**; Manos, M.M.; Glass, A.G.; Scott, D.R.; Sherman, M.E.; Buckland, J.; Lowy, D.; Schiller, J. (1996) Epidemiologic determinants of seroreactivity to human papillomavirus (HPV) type 16 virus-like particles in cervical HPV-16 DNA-positive and -negative women. J. Infect. Dis. 174(5):937-943.

Lörincz, A.T. (1996) Hybrid Capture™ method for detection of human papillomavirus DNA in clinical specimens: a tool for clinical management of equivocal Pap smears and for population screening. J. Obstet. Gynaecol. Res. 22(6):629-636.

Lörincz, A. (1997) Human papillomavirus testing. Pathology Case Reviews 2(1):43-48.

Sherman, M.E.; Schiffman, M.H.; **Lörincz, A.T.**; Herrero, R.; Hutchinson, M.; Bratti, C.; Zahniser, D,; Morales, J.; Hildesheim, A.; Helgesen, K.; Kelly, D.; Alfaro, M.; Mena, F.; Balmaceda, I.; Mango, L.; Greenberg, M. (1997) Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. Cancer 81(2):89-97.

Sherman, M.E.; Schiffman, M.H.; Mango, L.J.; Kelly, D.; Acosta, D.; Cason, Z.; Elgert, P.; Zaleski, S.; Scott, D.R.; Kurman, R.J.; Kiviat, N.B.; Stoler, M.; **Lorincz, A.T.** (1997) Evaluation of PAPNET testing as an ancillary tool to clarify the status of the "atypical" cervical smear. Mod. Pathol. 10(6):564-571.

Cope, J.U.; Hildesheim, A.; Schiffman, M.H.; Manos, M.M.; **Lörincz, A.T.**; Burk, R.D.; Glass, A.G.; Greer, C.; Buckland, J.; Helgesen, K.; Scott, D.R.; Sherman, M.E.; Kurman, R.J.; Liaw, K.-L. (1997) Comparison of the Hybrid Capture tube test and PCR for detection of human papillomavirus DNA in cervical specimens. J. Clin. Microbiol., 35(9):2262-2265.

Cullen, A.P.; Long, C.D.; **Lörincz, A.T.** (1997) Rapid detection and typing of herpes simplex virus DNA in clinical specimens by the Hybrid Capture II signal amplification probe test. J. Clin. Microbiol. 35(9):2275-2278.

Lörincz, A.T. (1997) Methods of DNA hybridization and their clinical applicability to human papillomavirus detection. In: New Developments in Cervical Cancer Screening and Prevention (Franco, E.; Monsonego, J., eds.), pp. 325-337. Blackwell Science, Oxford.

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Attachment A

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Attachment B

INVITED SPEAKER
INTERNATIONAL CONFERENCES

1. Bay Area Yeast Meeting. August 3, 1983. Berkeley, California.
2. Origin of Female Genital Cancer. April 14-17, 1985. Cold Spring Harbor, New York.
3. Workshop on Mechanisms of Transformation by Papillomaviruses. February 18-19, 1986. Bethesda, Maryland.
4. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. April 4-10, 1986. Sarasota, Florida.
5. Human Papillomaviruses and Cervical Carcinoma. Second International Conference. October 27-29, 1986. Chicago, Illinois.
6. Human Papillomaviral Infection and Lower Genital Tract Neoplasia. May 7-9, 1987. Atlanta, Georgia.
7. HPV Workshop - Type Consensus Meeting. March 22-23, 1988. New York, New York.
8. Human Papillomaviruses and Squamous Carcinoma. Third International Conference. October 24-26, 1988. Chicago, Illinois.
9. Impact of HPV Testing on Cervical Cancer Screening and Diagnosis. National Cancer Institute Sponsored Conference. February 2, 1989. Rockville, Maryland.
10. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. February 27-March 5, 1989. Sarasota, Florida.
11. UCLA Conference on Papillomaviruses. March 11-18, 1989. Taos, New Mexico.
12. An Update: Human Papillomavirus Infection. April 14, 1989. Lenexa, Kansas.
13. Fifth Annual Clinical Virology Symposium. April 30-May 3, 1989. Clearwater Beach, Florida.
14. Thirtieth Annual Meeting of the Japanese Clinical Cytology Society. June 14-16, 1989. Tokyo, Japan.
15. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. November 5-12, 1989. Sarasota, Florida.
16. Human Papillomavirus Infections—A Postgraduate Course. October 21-22, 1989. Washington, DC.
17. Diagnosis and Treatment of Vulvar, Vaginal and Cervical Disease - A Postgraduate Course. October 27-28, 1989. Washington, DC.
18. National Meeting of the Canadian Association for Clinical Microbiology and Infectious Diseases. November 26-30, 1989. Montreal, Canada.
19. Workshop on Development of STD Diagnostics for Resource-Poor Settings. February 7-8, 1990. Rosslyn, Virginia.
20. Sixth Meeting of the Scandinavian Society for Gynecological Medicine. September 6-8th, 1990. Mariehamn, Finland.
21. International Symposium on Diagnosis of Sexually Transmitted Diseases. August 16-17, 1991. Uppsala, Sweden.
22. Fourth International Conference on Human Papillomaviruses and Genital Carcinoma. September 17-19, 1990. Chicago, Illinois.
23. Second IARC Workshop on HPV and Cervical Cancer, November 25-28, 1991. Brussels, Belgium.
24. Fifth International Conference on Human Papillomavirus. October 25-28, 1992. Chicago, Illinois.
25. St. Joseph's Institute of Laboratory Medicine Symposium. April 29, 1993. London, Ontario, Canada.
26. Twelfth Annual High Technology R&D Trade Fair. May 10-11, 1993. Arlington, Virginia.
27. 8th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1993. Chicago, Illinois.
28. 1993 U.K. Wellcozyme Users Conference. June 17-18, 1993. St. Albans, England.

29. Steering Committee Meeting of the International Biological Study on Cervical Cancer. October 2, 1993. Baltimore, Maryland.
30. The American Society for Colposcopy and Cervical Pathology, in joint sponsorship with The Society of Canadian Colposcopists. March 22-26, 1994. Orlando, Florida.
31. 2nd International Congress of Papillomavirus in Human Pathology. April 6-8, 1994. Paris, France.
32. Novel Amplification Technologies for DNA/RNA-Based Diagnostics. April 20-22, 1994. San Francisco, California.
33. First Congress on Papillomavirus of the Catholic Cancer Center. May 7, 1994. Seoul, Korea.
34. The Feasibility of Genetic Technology to Close the HIV Window in Donor Screening (US FDA workshop) September 26-28, 1994. Silver Spring, Maryland.
35. Nucleic Acid-Based Technology: Revolution in Clinical Diagnosis, Applications and Research. November 7-9, 1994. Amsterdam, The Netherlands.
36. Nucleic Acid-Based Technologies: Current Challenges, Future Strategies, and End User Perspectives. May 31-June 2, 1995. San Francisco, California.
37. Murex Users' Meeting. June 7-8, 1995. London, United Kingdom.
38. Eleventh Meeting of the International Society for STD Research, August 27-30,1995. New Orleans, Louisiana.
39. X Congresso Brasileiro - II Congresso Latino Americano de Patologia do Trato Genital Inferior e Colposcopia. September 20-24, 1995. Sao Paulo, Brazil.
40. Workshop organized by Murex Diagnostica GmbH. October 12, 1995. Zurich, Switzerland.
41. XVth Asian and Oceanic Congress of Obstetrics and Gynecology. October 15-20, 1995. Bali, Indonesia.
42. Gene Quantification: Diagnosis, Monitoring & Drug Development. February 26-27, 1996. San Diego, California.
43. VIII Curso Internacional de Cancer Cervico Uterino y Lesiones Premalignas. March 7-9, 1996. Mexico City, Mexico.
44. Gene Detection: Diagnostic Technology for Infectious Agents and Human Genetic Diseases. May 2-3, 1996. Coronado, California.
45. 9th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1996. Sydney, Australia.
46. EUROGIN-WHO International Joint Experts Meeting "Cervical Cancer Screening and New Developments. June 17-19, 1996. Geneva, Switzerland.
47. State of Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning. August 9, 1996. Annapolis, MD.
48. Advances in Nucleic Acid Amplification & Detection. September 18-19, 1996. Amsterdam, The Netherlands.
49. IV Simposio International e III Jornada Baiana de Patologia do Trato Genital Inferior e Colposcopia. October 3-6, 1996. Salvador, Brazil.
50. The American Society for Microbiology, New York City Branch, & St. John's University. November 1, 1996. Jamaica, New York.
51. XIII Latin American Microbiology Congress. November 5-9, 1996. Caracas, Venezuela.
52. Workshop on Cervical Cancer Screening Program. November 6-7, 1996. Juquei, SP, Brazil.
53. EUROGIN-WHO 3rd International Congress on Lower Genital Tract Infections and Neoplasia: Future Challenges and Strategies. March 25-28, 1997. Paris, France.
54. 15th Annual Reproductive Health Update, co-sponsored by the Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning, Anne Arundel Community College, and Planned Parenthood. April 25, 1997. Arnold, MD.
55. Symposium on HPV Infection and Cervical Cancer. May 11, 1997. Seoul, Korea.
56. HPV workshop. May 16, 1997. Taipei, Taiwan, R.O.C.
57. XV FIGO World Congress of Gynecology and Obstetrics. August 3-8, 1997. Copenhagen, Denmark.

58. HPV Testing: European Perspectives on Cervical Neoplasia Prevention, Prognosis and Management. November 13-15, 1997. Geneva, Switzerland.
59. European HPV Clinical Summit Meeting. January 29-30, 1998. Vienna, Austria.
60. IV Reunión Nacional de Colposcopia y Patologia Cervical. February 19-21, 1998. Guadalajara, Mexico.
61. Gene Quantification: Clinical Applications and Drug Development. March 30-April 1, 1998. San Diego, CA.
62. Biennial Meeting, American Society for Colposcopy and Cervical Pathology. March 30-April 2, 1998. Scottsdale, AZ.
63. ASCP/CAP Spring Meeting. April 4-8, 1998. Los Angeles, CA.
64. 8th European Course on HPV-Associated Pathology. April 22-24, 1998. Munich, Germany.
65. DNA/RNA Diagnostics. May 19-21, 1998. Washington, DC.
66. Microbial-Linked Diseases: Shifting the Pathogenic Paradigm. June 25-26, 1998. San Diego, CA.
67. Human Papillomavirus Infections and Cervical Cancer. July 7-11, 1998. Montreal, Canada.
68. Simposio Internacional sobre HPV: IV Curso de Atualizacao em Patologia do Trato Genital Preparatorio para Concurso de Qualificacao em Colposcopia. September 3-4, 1998. Belo Horizonte, Brazil.
69. IIIer Congreso Lainoamericano y IIdo Congreso Paraguayo de Patologia del Tracto Genital Inferior y Colposcopia. September 7-11, 1998. Asuncion, Paraguay.
70. 17th International Papillomavirus Conference. January 9-15, 1999. Charleston, SC.
71. INCGC - Consensus Conference on Cervical Cancer Screening and Management. January 28-31, 1999. Tunis, Tunisia.
72. HPV Summit 1999: New Approaches to the Detection and Elimination of Cervical Cancer. February 8-10, 1999. Chamonix, France.
73. Centers for Disease Control and Prevention and American Cancer Society External Consultants' Meeting: Prevention of Genital HPV Infection and Sequelae. April 13-14, 1999. Atlanta, GA.
74. 11th International Meeting of Gynaecological Oncology. May 8-12, 1999. Budapest, Hungary.
75. 4th Scientific Meeting on Primary and Secondary Prevention of Gynecological Cancer. May 14-16, 1999. Thessaloniki, Greece.
76. 13th Meeting of the International Society for Sexually Transmitted Diseases Research. July 11-14, 1999. Denver, CO.
77. Reproductive Health '99. September 22-25, 1999. New York. NY.
78. 1999 ASCP/CAP Fall Meeting. September 25-30, 1999. New Orleans, LA.
79. 10th World Congress of Cervical Pathology & Colposcopy. November 7-11, 1999. Buenos Aires, Argentina.
80. North American Sexual Health Management Symposium. November 21-23, 1999. New York, NY.
81. Cervical and Breast Cancer in the Next Millenium. December 3-6, 1999. Mexico City, Mexico.
82. XI Encontro de Atualização em Patologia do Trato Genital Inferior e Colposcopia – Cervicolp' 2000. March 23-25, 2000. Sao Paulo, Brazil.
83. EUROGIN 2000: Global Challenge of Cervical Cancer Prevention. April 4-9, 2000. Paris, France.
84. ASCP/CAP Spring Meeting. April 9-12, 2000. Boston, MA.
85. Clinical Implications Conference 1: "Role of Human Papillomavirus in Cervical Neoplasia." April 28-29, 2000. Chicago, IL.
86. 26th National Meeting of the Clinical Ligand Assay Society. May 31-June 2, 2000. Boston, MA.
87. Meeting of the Pathological Society of Great Britain and Ireland. July 12-14, 2000. Nottingham, UK.
88. 7th International Meeting of Genital Tract Pathology & Colposcopy. October 25-30, 2000. Belo Horizonte, Brazil.

Attachment C

INVITED SPEAKER
DEPARTMENTAL SEMINARS

1. Heidelberg Cancer Research Center, Heidelberg, Germany, November, 1985.
2. Columbia Hospital for Women, Washington, DC, December, 1985, 1986, and 1991.
3. Fred Hutchinson Cancer Research Center, Seattle, Washington, July, 1988.
4. Johns Hopkins Medical Institutions, Baltimore, Maryland, November, 1990.
5. University of New Hampshire, Department of Microbiology, October, 1991.
6. Sharp Memorial Hospital OB/GYN Department, San Diego, California, November 11, 1993.
7. Prodia Laboratory, Jakarta, Indonesia, May 3, 1994.
8. Bio-Check Laboratories Ltd. Pathology, Diagnostic Virus, and Gynecology Departments, Taipei, Taiwan, R.O.C., May 5, 1994.
9. University College Hospital Virology Department, London, United Kingdom, June 16, 1995.
10. John Radcliffe Infirmary Pathology Department, Oxford, United Kingdom, June 17, 1995.
11. National Cancer Hospital Cytology Department, Oslo, Norway, October 10, 1995.
12. Columbia Hospital for Women Pathology Department, Washington, DC, October 24, 1995.
13. Associated Regional University Pathologists (ARUP), Salt Lake City, UT, February 28, 1996.
14. Washington Hospital Center, Transplant Surgery Department, March, 1996.
15. Health Insurance Plan of New York, Jericho, NY, April 24, 1996.
16. Friedrich Schiller University Department of Obstetrics and Gynecology, Jena, Germany, May 8, 1996.
17. Unilab KPT/ Murex Diagnostica GmbH, HPV workshop for gynecologists/venerologists/ pathologists/virologists, Budapest, Hungary, May 10, 1996.
18. Long Island Jewish Medical Center Gynecology Department, New York, NY, June 5, 1996.
19. Washington Gynecological Society, Washington, DC, January 8, 1997.
20. Hyundei Medical Center, Seoul, Korea, May 10, 1997.
21. Seoul National University, Seoul, Korea, May 12, 1997.
22. Papanicolaou Institute, Buenos Aires, Argentina, July 14-16, 1997.
23. Doctors' meeting convened by Murex Central Europe, Vienna, Austria, November 17, 1997.
24. One seminar and one grand rounds, for the departments of Gynecologic Oncology, Biochemistry & Molecular Genetics, and Infectious Diseases at the University of Alabama at Birmingham, December 9-10, 1998.
25. Maryland Bioscience Alliance, High Technology Council of Maryland, Rockville, MD, January 21, 1999.
26. University of Rochester Research Symposium on Human Papillomavirus Infections from the Bench to the Bedside, Rochester, NY, April 30, 1999.
27. Women's Health Task Force Meeting, Washington, DC, February 29-March 1, 2000.
28. Maryland Bioscience Alliance Cancer Forum, High Technology Council of Maryland, Rockville, MD, March 22, 2000.
29. Gynecologic Cancer Translational Research Retreat, Chantilly, VA. May 5-6, 2000.
30. 18th Annual Reproductive Health Update for the Maryland Department of Health, Annapolis, MD. May 19, 2000.
31. Georgetown University Department of Pathology, Washington, DC. May 25, 2000.
32. Cleveland Clinic Foundation, Cleveland, OH. June 30, 2000.

33. University of Medicine and Dentistry of New Jersey, Scotch Plains, NJ. October 13, 2000.